UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,980	04/07/2005	Andrea Amalfitano	180/151 PCT/US	7130

25297 7590 08/04/2009

JENKINS, WILSON, TAYLOR & HUNT, P. A.
Suite 1200 UNIVERSITY TOWER
3100 TOWER BLVD.,
DURHAM, NC 27707

EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
08/04/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,980	AMALFITANO ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-9 and 16-148* is/are pending in the application.

4a) Of the above claim(s) *8,16,24,25,29,34,37-144 and 148* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-7,9,17-23,26-28,30-33,35,36 and 145-147* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/13/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' amendment and submission filed on May 18, 2009 that includes a response to the Office action dated November 17, 2008, has been entered. Claim 2 and 7 have been amended, claims 12-15 cancelled, and claims 143-148 newly added. Accordingly, claims 1-3, 5-9, and 16-148 are pending in the application. Claims 8, 16, 24, 25, 29, 34 and 37-142 stand withdrawn from further consideration, without traverse, as drawn to non-elected inventions and species of the invention. New claims 143, 144 and 148 are hereby withdrawn from further consideration, as directed to non-elected subject matter (i.e. E1a as a functional genomic region and host cell stably modified to express a functional pol or pTP polypeptide). The claims have been examined commensurate in scope with the elected invention, and the species of the invention. Applicants are directed to the elections made in their response dated December 3, 2007.

Claims 1-3, 5-7, 9, 17-23, 26-28, 30-33, 35, 36 and 145-147 are under current examination.

Withdrawn Objection to the Specification/Abstract

The abstract was objected to in the previous Office action dated November 17, 2008 as presented with deleted text. Applicants have supplied a new abstract, as a clean copy apart from other text, in accordance with 37 CFR 1.52(b)(4), obviating the ground for objection. Thus, the objection is hereby withdrawn.

Withdrawn Claim Rejections - 35 USC § 112- New Matter

Claim 15 was rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement, and introducing new matter into the disclosure, in the previous Office action dated November 17, 2008. Applicants' cancellation of the claim renders the rejection moot. Thus, the rejection is hereby withdrawn.

Response, Maintained & New Claim Rejections - 35 USC § 103

Claims 1-3, 5-7, 9, 17-22, 26, 27, 35 and 36 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lieber et al. (J. Virol. 73(11):9314-9324; 1999), in view of Mountz et al. (U.S. Patent No.: 6,383,794, filed Aug. 24, 1999). Applicants' cancellation of claims 12-15 renders their rejection moot. The rejection set forth on pp. 5-8 of the previous Office action dated November 17, 2008 is maintained for claims 1-3, 5-7, 9, 17-22, 26, 27, 35 and 36 and further applied to new claims 145-147 for reasons of record.

The rejection is re-iterated as follows:

The claims embrace a recombinant adenovirus/AAV hybrid virus comprising an adenovirus vector genome deleted in the polymerase region, or the preterminal protein region, or both; comprising AAV2 inverted terminal repeats (ITRs) and cis-elements for viral replication, packaging and encapsidation, and a functional adenovirus E4orf6 region, further comprising a heterologous nucleic acid sequence, and wherein the AAV genome does not encode the AAV rep or AAV capsid proteins, and wherein the vector genome encodes an AAV rep protein operably linked to the AAV p5 promoter; and wherein the hybrid virus can complete viral replication in a helper cell that provides AAV Rep and Cap.

Lieber et al. describe integrating adenovirus-AAV hybrid vectors devoid of all viral genes (Title). Further teaching that ITRs inserted into adenovirus (Ad) vector genomes resulting in vector genomes devoid of all viral genes, are efficiently packaged into functional Ad capsids (Abstract). The Ad vectors contain AAV ITRs flanking a reporter gene cassette inserted into the E1 region; Ad.AAV vector genomes contain only the transgene flanked by AAV ITRs, and

packaging signals (Abstract; the reporter transgene corresponding to a heterologous nucleic acid, limitation of claim 1(b)).

In Figure 1, Lieber et al. depict an Ad.AAV2 hybrid vector comprising a neo gene under the control of the SV40 and Tn5 promoters (limitation of claims 21, 22 and 27). As the hybrid vector genome does not include coding sequence for any adenoviral or AAV proteins, it necessarily comprises deletions of the adenovirus polymerase and preterminal protein regions (limitation of claims 17-20); and does not encode AAV Rep or AAV capsid proteins (limitation of claim 1 (b)), or E1 region products (limitation of claims 12 and 14). Lieber et al. additionally teach hybrid vectors containing the AAV2 genome ITRs (second column, p. 9315, Figure 1, and first column, first paragraph, p. 9317; limitation of claim 3).

With regard to replication and production of hybrid virus in a helper cell, Lieber et al teach that viruses with different transgene cassettes incorporated into their E1 regions were generated by recombination of pXCJL1-derived shuttle plasmids and pJM17 (Microbix) in 293 cells; thus constituting a helper cell. Viruses containing two AAV ITRs tended to have deletions within the ITRs or other Ad sequences and to recombine with Ad sequences present within the 293 cell genome. Only plaques from viruses with intact ITRs were amplified, CsCl banded, and tittered (first column, p. 9315, under Adenoviruses; limitation of claims 35 and 36).

While Lieber et al. do not describe their hybrid virus as comprising a functional E4orf6 region, such variation in the construction of AAV hybrid vectors was known in the prior art.

Mountz et al. disclose high titer recombinant AAV hybrid vectors encoding a therapeutic gene flanked by ITRs of AAV and the AAV rep and cap genes (Abstract). In Example 1, Mountz et al. describe the construction of the hybrid Ad-AAV vector, by cloning the 4.2 kb Xba fragment of AAV pSub201 containing the AAV rep and cap genes into the E1 Xba site of an adenoviral shuttle vector (column 13). The pSub201 is an infectious clone of AAV type 2 DNA. The rep and cap genes are under the control of the AAV p5 promoter in the hybrid AdAAV vector, as shown in Fig. 1A (column 4; limitation of claims 6 and 7).

The recombinant AAV further comprises the adenoviral ITRs and an adenovirus packaging signal, EI, E2A, E4 and VIA regions and no other adenoviral gene regions (see Fig.

15B, pages 42-44; limitation of claims 2). Mountz et al. state: "Preferably, the adenovirus genome is deleted for all coding sequences other than those genes required for adenoviral replication. More preferably, the genes required for adenoviral replication, and hence remaining on the adenoviral genome, are E1A, E1B, E2A, E4 and VIA." (column 7, last paragraph; limitation of claim 10). As the recombinant hybrid vector does not contain an E2B region, it necessarily is deficient in sequences encoding the preterminal and polymerase protein regions (limitation of claims 1(a) and 17-20). Further, the E4 region contains the E4orf6 (limitation of claim 1(a)), thus curing the deficiency in Lieber et al. The insertion of the genes required for replication is into an E1 deleted region of the vector (shown in Figs. 10 and 11; limitation of claims 12 and 13).

Mountz et al. describe AdAAV viruses that express the cap and rep genes separately , to separately modulate their expression (column, 17, lines 4-7); Additionally teaching the use of a stable cell line which constitutively expresses the rep and cap genes to provide rAAV packaging function (column 19, lines 20-22; limitation of claim 147). In Example 12, column 18, Mountz et al. state: "The helper-dependent recombinant adenoviruses, including AdrAAV8kb (FIG. 10B) and AdrAAV-GFP8kb (FIG. 10C) which produces high-titer, Ad-free rAAV, was constructed by deleting an 8 Kb PmeI-SgfI fragment encoding the Ad hexon, penton, core protein, and DNA polymerase genes from plasmid pAdAAV or pAdrAAV-GFP (FIG. 1A, FIG. 4A). This virus already has deletions in the E1 and E3 genes. Both constructs are able to replicate and be packaged in the presence of the Ad helper virus, AdLoxpTK, in 293CreNS cells." (limitation of claims 35 and 36).

In Example 4, column 13, Mountz et al. describe the construction of a hybrid AdrAAV vector encoding a GFP protein operably linked to the CMV promoter (the GFP constituting a heterologous reporter polypeptide; limitation of claims 21 and 22, 26 and 27).

The teachings of Lieber et al. and Mountz et al. are both directed to hybrid adeno/AAV vectors. Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine their respective teachings and to include a functional adenovirus E4orf6 region in the hybrid vector of Lieber et al., with a reasonable expectation of success, at the time of the instant invention. A person of ordinary skill in the art would construct such a hybrid adeno/AAV

vector as a matter of design choice, which amounts to combining prior art elements according to known methods to yield predictable results. Applicants should note that the *KSR* case forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. *KSR International Co. v. Teleflex Inc.*, 550 U.S.-, 82USPQ2d 1385 (2007).

Response to Arguments:

Applicants traverse, arguing Lieber and Mountz are not combinable because the goal in Lieber is to produce an Ad-AAV hybrid vector devoid of all viral genes; that Lieber reference states "this hybrid vector should be devoid of all Ad genes whose expression may cause immunological or toxic side effects"; that Lieber teaches against a vector comprising a functional E4orf6 region, and thus one of ordinary skill in the art would not look to Mountz to "add back" any viral genes. Applicants' arguments have been fully considered, but are not found persuasive.

In response, it should be noted that the instant obviousness rejection is not based on a strict TSM test (requiring a specific teaching, suggestion or motivation) to combine the references. As previously indicated, a person of ordinary skill in the art would construct the instantly claimed hybrid adeno/AAV vector as a matter of design choice, which amounts to combining prior art elements according to known methods to yield predictable results. A person of ordinary skill in the art would be apprised of the totality of the prior art, that include the teachings of Mountz et al., that have been ignored by Applicants.

Lieber et al. demonstrate that the Ad-AAV hybrid vector may be produced by deletion of viral proteins that may have toxic side effects. Lieber et al. state: "The concept of combining elements from different viruses is not new" (second column, p. 9322). While Lieber et al. do not specify which Ad genes may cause toxic side effects, Mountz et al. state in Example 3, column 13 that while previous investigators have proposed expression of AAV rep genes might be toxic to cells, the results indicate that the previous failures to produce AdAAV viral particles may have been due to unidentified factors. Mountz et al. state: "Preferably, the adenovirus genome is deleted for all coding sequences other than those genes required for adenoviral replication. Thus, all structural and capsid proteins have been deleted from the vectors of Mountz et al. Further, the

instantly claimed hybrid vector is devoid of all functional adenovirus genes, except for E4orf6, and there is no indication in either the teachings of Lieber et al. or Muntz et al. to implicate the E4orf6 region as toxic. Thus, there is no teaching in Lieber against a vector comprising a functional E4orf6 region, as asserted by Applicants.

With reference to the KSR case, Applicants argue that KSR stands for the proposition that "A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art". In response, it should be noted that the instant rejection is predicated on more that knowledge of each element in the prior art. AdAAV hybrid vectors comprising deletions in all viral genes except for those required for replication are specifically disclosed by Mountz et al., and Lieber et al. further indicate that additional deletions of Ad genes can also be made in an AdAAV hybrid vector.

Thus, the rejection is maintained for claims 1-3, 5-7, 9, 17-22, 26, 27, 35 and 36 and further applied to new claims 145-147 for reasons of record and the foregoing discussion.

Claims 1 and 21-23 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lieber et al. (J. Virol. 73(11):9314-9324; 1999), in view of Mountz et al. (U.S. Patent No.: 6,383,794, filed Aug. 24, 1999), and further in view of Souza et al. (U.S. Patent Application Publication No.: 2003/0017139; effective filed Nov. 16, 1999). The rejection set forth on pp. 8-10 of the previous Office action dated November 17, 2008 is maintained for reasons of record.

The rejection is re-iterated as follows:

The claims encompass a recombinant adenovirus/AAV hybrid virus comprising an adenovirus vector genome deleted in the polymerase region, or the preterminal protein region, or both; comprising AAV2 inverted terminal repeats (ITRs) and cis-elements for viral replication, packaging and encapsidation, and a functional adenovirus E4orf6 region, further comprising a heterologous nucleic acid sequence that is operatively associated with a liver-specific promoter, and wherein the AAV genome does not encode the AAV rep or AAV capsid proteins, and wherein the vector genome encodes an AAV rep protein operably linked to the AAV p5 promoter.

Lieber et al. describe integrating adenovirus-AAV hybrid vectors devoid of all viral genes (Title). Further teaching that ITRs inserted into adenovirus (Ad) vector genomes resulting in vector genomes devoid of all viral genes, are efficiently packaged into functional Ad capsids (Abstract). The Ad vectors contain AAV ITRs flanking a reporter gene cassette; Ad.AAV vector genomes contain only the transgene flanked by AAV ITRs, and packaging signals (Abstract; the reporter transgene corresponding to a heterologous nucleic acid, limitation of claim 1(b)).

In Figure 1, Lieber et al. depict an Ad.AAV2 hybrid vector comprising a neo gene under the control of the SV40 and Tn5 promoters. As the hybrid vector genome does not include coding sequence for any adenoviral or AAV proteins, it necessarily comprises deletions of the adenovirus polymerase and preterminal protein regions (limitation of claim 1(a) (i-iii)). Lieber et al. additionally teach hybrid vectors containing the AAV2 genome ITRs (second column, p. 9315, Figure 1, and first column, first paragraph, p. 9317). The Ad.AAV vectors are described as a promising tool for stable gene transfer *in vitro* and *in vivo* (Abstract).

Mountz et al. disclose high titer recombinant AAV hybrid vectors encoding a therapeutic gene flanked by ITRs of AAV and the AAV rep and cap genes (Abstract). The recombinant AAV further comprises the adenoviral ITRs and an adenovirus packaging signal, El, E2A, E4 and VIA regions and no other adenoviral gene regions (see Fig. 15B, pages 42-44; limitation of claims 2). Mountz et al. state: "Preferably, the adenovirus genome is deleted for all coding sequences other than those genes required for adenoviral replication. More preferably, the genes required for adenoviral replication, and hence remaining on the adenoviral genome, are E1A, E1B, E2A, E4 and VIA." (column 7, last paragraph; limitation of claim 10). As the recombinant hybrid vector does not contain an E2B region, it necessarily is deficient in sequences encoding the preterminal and polymerase protein regions (limitation of claims 1(a) and 17-20). Further, the E4 region contains the E4orf6 (limitation of claim 1(a)). In Example 4, column 13, Mountz et al. describe the construction of a hybrid AdrAAV vector encoding a GFP protein operably linked to the CMV promoter (the GFP constituting a heterologous reporter polypeptide; limitation of claims 21 and 22).

While Lieber et al. and Mountz et al. do not describe their hybrid AAV vectors encoding a heterologous nucleic acid as operatively associated with a liver-specific promoter, such promoters were known in the prior art.

Souza et al. describe adeno-associated viral vectors comprising liver specific enhancer/promoter combinations linked to a transgene administered to recipient cells (Abstract). The references of Lieber et al., Mountz et al. and Souza et al. are all directed to the use of recombinant AAV vectors for transfer of heterologous transgenes genes to recipient cells. Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to use the liver-specific promoter of Souza et al. in the hybrid AAV vector of Lieber et al. or Mountz et al. for gene transfer, with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would be motivated to utilize the hybrid AAV vector of Lieber et al. or Mountz et al. for transfer of transgene operably linked to a liver-specific promoter for therapy, because such vectors could be produced at high titer and high purity (see Abstract, Lieber et al).

Response to Arguments:

Applicants traverse, arguing that Lieber in view of Mountz fails to disclose or suggest a hybrid virus that comprises Ad E4orf6 as well as a deletion of pol and/or pTP; and Souza does not disclose or suggest a vector that encodes E4orf6, thus failing to cure the deficiency of Lieber in view of Mountz. Applicants' arguments have been fully considered, but are not found persuasive.

In response, it should be noted that Mountz et al. describe their vectors as having deletions in all genes, except for, E1A, E1B, E2A, E4 and VIA." (column 7, last paragraph); and the E4 region necessarily contains the E4orf6 region. Lieber et al. describe Ad-AAV hybrid vector that can be devoid of all viral genes (Title). As the hybrid vector genome does not include coding sequence for any adenoviral or AAV proteins, it necessarily comprises deletions of the adenovirus polymerase and preterminal protein regions. Thus, there is no requirement for Souza et al. to teach or suggest the same.

Thus, the rejection is maintained for reasons of record and the foregoing commentary.

Claims 1, 26-28 and 30-33 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lieber et al. (J. Virol. 73(11):9314-9324; 1999), in view of Mountz et al. (U.S. Patent No.: 6,383,794, filed Aug. 24, 1999), and further in view of Podsakoff et al. (U.S. Patent No.: 5,962,313; effective filed Jan. 16, 1997). The rejection set forth on pp. 10-12 of the previous Office action dated November 17, 2008 is maintained for reasons of record.

The rejection is re-iterated as follows:

The claims encompass a recombinant adenovirus/AAV hybrid virus comprising an adenovirus vector genome deleted in the polymerase region, or the preterminal protein region, or both; comprising AAV2 inverted terminal repeats (ITRs) and cis-elements for viral replication, packaging and encapsidation, and a functional adenovirus E4orf6 region, further comprising a heterologous nucleic acid sequence encoding human lysosomal acid α-glucosidase, and wherein the AAV genome does not encode the AAV rep or AAV capsid proteins, and wherein the vector genome encodes an AAV rep protein operably linked to the AAV p5 promoter.

The instant specification identifies glycogen storage disease type II (GSD II) as a classical lysosomal storage disorder, mediated by Acid α-Glucosidase (second paragraph p. 2).

Lieber et al. describe integrating adenovirus-AAV hybrid vectors devoid of all viral genes (Title). Further teaching that ITRs inserted into adenovirus (Ad) vector genomes resulting in vector genomes devoid of all viral genes, are efficiently packaged into functional Ad capsids (Abstract). The Ad vectors contain AAV ITRs flanking a reporter gene cassette; Ad.AAV vector genomes contain only the transgene flanked by AAV ITRs, and packaging signals (Abstract; the reporter transgene corresponding to a heterologous nucleic acid, limitation of claim 1(b)).

In Figure 1, Lieber et al. depict an Ad.AAV2 hybrid vector comprising a neo gene under the control of the SV40 and Tn5 promoters (constituting a reporter polypeptide; limitation of claims 26 and 27). As the hybrid vector genome does not include coding sequence for any adenoviral or AAV proteins, it necessarily comprises deletions of the adenovirus polymerase and preterminal protein regions (limitation of claim 1(a) (i-iii)). Lieber et al. additionally teach hybrid vectors containing the AAV2 genome ITRs (second column, p. 9315, Figure 1, and first column, first paragraph, p. 9317). The Ad.AAV vectors are described as a promising tool for stable gene transfer *in vitro* and *in vivo* (Abstract).

Mountz et al. disclose high titer recombinant AAV hybrid vectors encoding a therapeutic gene flanked by ITRs of AAV and the AAV rep and cap genes (Abstract). The recombinant AAV further comprises the adenoviral ITRs and an adenovirus packaging signal, El, E2A, E4 and VIA regions and no other adenoviral gene regions (see Fig. 15B, pages 42-44; limitation of claims 2). Mountz et al. state: "Preferably, the adenovirus genome is deleted for all coding sequences other than those genes required for adenoviral replication. More preferably, the genes required for adenoviral replication, and hence remaining on the adenoviral genome, are E1A, E1B, E2A, E4 and VIA." (column 7, last paragraph; limitation of claim 10). As the recombinant hybrid vector does not contain an E2B region, it necessarily is deficient in sequences encoding the preterminal and polymerase protein regions (limitation of claims 1(a) and 17-20). Further, the E4 region contains the E4orf6 (limitation of claim 1(a)).

While Lieber et al. and Mountz et al. do not describe their hybrid AAV vector heterologous protein as human lysosomal acid α-glucosidase, the prior art had taught AAV vectors carrying a nucleic acid encoding for lysosomal acid α-glucosidase.

Podsakoff et al. describe AAV vectors comprising a gene encoding a lysosomal enzyme (Title). In Example 8 (column 27), Podsakoff et al. describe *in vitro* and *in vivo* transduction of muscle cells using a rAAV-hGAA vector encoding human lysosomal acid α-glucosidase to treat glycogen storage type II (Pompe's disease) (columns 27 and 28; limitation of claims 28 and 30-33).

The references of Lieber et al., Mountz et al. and Podsakoff et al. are all directed to the use of recombinant AAV vectors for transfer of heterologous genes *in vitro* and *in vivo*. Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to use the human lysosomal acid α-glucosidase of Podsakoff et al. in hybrid AAV vectors for gene transfer, with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would be motivated to utilize the hybrid AAV vectors for transfer of the human lysosomal acid α-glucosidase transgene for therapy, because such vectors could be produced at high titer and high purity (see Abstract, Lieber et al).

Response to Arguments:

Applicants traverse, arguing that Lieber in view of Mountz fails to disclose or suggest a hybrid virus that comprises Ad E4orf6 as well as a deletion of pol and/or pTP; and Podsakoff does not disclose or suggest a vector that encodes E4orf6, thus failing to cure the deficiency of Lieber in view of Mountz. Applicants' arguments have been fully considered, but are not found persuasive.

Applicants are directed to the response provided above. Thus, the rejection is maintained for reasons of record and the foregoing commentary.

Response to Arguments Regarding New Claims:

As indicated above, new claims 143, 144 and 148 are withdrawn from further consideration, as directed to non-elected subject matter (i.e. E1a as a functional genomic region and host cell stably modified to express a functional pol or pTP polypeptide). The claims have been examined commensurate in scope with the elected invention, and the species of the invention. Applicants are directed to the elections made in their response dated December 3, 2007. Thus, the E1a region as a functional region has not been examined for determination of patentability.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Primary Examiner, Art Unit 1633